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Third-line Antiretroviral Therapy in a Nigerian Clinic: Case Series

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Abstract

There is limited experience with use of third line regimen in sub-Saharan Africa. It is expected that about 10% of those on 1st line treatment will fail and to be switched to 2nd line. Another 10% of those on 2nd line are also expected to fail and be switched to 3rd line. Recommendation for 3rd line in the guidelines is to include new drugs with minimal risk of cross resistance to previously used regimens such as Integrase Inhibitors and second-generation NNRTIs and PIs. We present three cases on third-line regimen on boosted Darunavir, Etravirine and Raltegravir. 66.7% viral suppression was achieved after four years of access to the medication. The third line regimen was well tolerated by the three cases and there was no report of serious adverse drug reaction. Adherence was also good in all cases. Third line regimen is effective but there is need to secure access. The cases reported had to interrupt treatment because access to free third-line ART was terminated by implementing partners. The Nigerian government is encouraged to take up the responsibility to provide third line regimen.

Keywords: Third-line antiretroviral therapy; Regimen; Nigeria

Rationale for Third-line Antiretroviral Therapy

The strategy of antiretroviral therapy (ART) employed in Nigeria is Highly Active Antiretroviral Therapy (HAART) as recommended by the World Health Organization (WHO) [1]. HAART is the combination of 3 or more ARVs from at least 2 different classes [2]. The goal of HAART is to achieve undetected viral load (VL) within 6 months of starting therapy and maintaining this for the rest of the patient's life [3].

The human immunodeficiency virus (HIV) undergoes high level of viral replication and turn over which lack proofreading mechanism [4]. This leads to generation of a large number of genetically distinct HIV variants or mutants. Mutation is change in nucleic acid sequence that results in a change in structure or function of the nucleic acid or a resulting protein [5]. Viral mutation is the primary culprit for resistance in HIV. Resistance could lead to treatment failure [6].

The emergence of resistance to antiretroviral medicines (ARVs) is an inevitable consequence of expanding access to ART [7]. It is expected that about 10% of those on 1st line treatment will fail and to be switched to 2nd line [8]. Another 10% of those on 2nd line are also expected to fail and be switched to 3rd line. The National guideline on ART makes recommendation for 1st and 2nd and 3rd line therapies. 3rd line (salvage therapy) therapy refers to treatment regimens designed for patients who have failed 1st and 2nd line regimens [9].

First line regimen recommended by the 2016 Nigerian HIV Care and Treatment Guidelines [9] is the use of non-nucleoside reverse transcriptase inhibitors (NNRTI) and 2 Nucleoside reverse transcriptase inhibitors (NRTI). The preferred first line being a combination of efavirenz (EFV 600 mg)+Lamivudine (3TC 150 mg)+Tenofovir (TDF 300 mg).

Recommendation for second line regimen is to substitute the NNRTI for a boosted protease inhibitor (either Lopinavir or Atazanavir) and introducing a new nucleoside while retaining Lamivudine. Zidovudine or Abacavir will replace TDF, but for patients whose first line regimen is Nevirapine+Lamivudine +Zidovudine (the recommended alternate first line regimen); the nucleosides in the second line regimen will be TDF and 3TC or Abacavir (ABC) and 3TC.

Recommendation for 3rd line in the guidelines is to include new drugs with minimal risk of cross resistance to previously used regimens such as Integrase Inhibitors and second-generation NNRTIs and PIs [9]

Patients who acquire or are primarily infected with HIV drug-resistant viruses have fewer treatment options. They are also at increased risk of morbidity and mortality, particularly in developing countries where choices for ART are limited. Understanding this limitation can help clinicians avoid minimally active ARVs in favor of more active ARVs, thereby avoiding treatment failure.

The three cases presented below were seen at the out Patients' Clinic of Nigerian Institute of Medical Research, Lagos; a care and treatment centre for HIV which have a cumulative of over 20,000 registered patients.

Case Details and Demographic Information

First patient

Mr S.A a 49 years old male trader with date of Birth 6th of March 1956, presented on the 28th of October 2005 for enrolment at the HIV treatment centre. Partner is also HIV positive. He had previously been on treatment for HIV infection for 3 years; he was first started on antiretroviral drugs Zidovudine (AZT), Lamivudine (3TC) and Nelfinavir which was later changed to Nevirapine (NVP), Lamivudine and Zidovudine by another physician. He was found to develop a rash in reaction to NVP. This was stopped and a drug resistance test was done where he was found to be susceptible to the following drugs Didanosine (ddl), Tenofovir (TDF), Nelfinavir (NFV) and was placed on this regimen. On this regimen the VL did not come down much and so he was referred to our centre for further evaluation and treatment. Patient had Hypertension at enrolment. He neither smoked nor drank alcohol.

At enrolment a HIV rapid test was done where he was found to be HIV-1 positive. He was changed to boosted lopinavir (LPV/r), Tenofovir (TDF and didanosine (ddl-EC 250 mg). His CD4 count at enrolment was 11 cells/mm^3, Viral load (VL) was done on the 27th of April 2006 and it was 29,524 RNA copies/ml From the time of enrolment his CD4 count fluctuated a lot and it was always below 250 till the 5th of February 2009 when it became 251 cells/mm^3 and VL was 547 RNA copies/ml. During this period he had only three results that showed undetectable VL levels but these results were not maintained showing elevated VL intermittently **(Table 1).**

Table 1: The drug substitutions that took place and tests that informed the decisions.

Sl No.	Start date of new Regimen	New Regimen	Date of Tests	VL (copies/ml)	CD (cells/mm^3)
1	22th of May 2006	LPV/r, TDF, 3TC, AZT	27th of April 2006	29524	72
2	2nd of October 2007	LPV/r, TDF, FTC, AZT	2nd of October 2007	5737*	148*
3	8th of January 2009	LPV/r, ABC, 3TC (reduced dose), AZT	8th of January 2009	Elevated Serum Creatinine Levels to 405 µmol/L Caused this Substitution	
*The viral load here increased from an undetectable level and CD4 count level here had dropped.					

It is important to note that the patients' Serum creatinine levels started increasing on the 27th of October 2008 from 270 µmol/L to what was observed in the table. It was on the 11th of June 2009 after series of tests, he was diagnosed to have HIVAN. However on the 29th of January 2010 he had a drug switch to a third line regimen of Darunavir (DRV), Ritonavir (TRV), Etravirine (ETR), and Raltegravir (RAL). He was able to maintain this undetectable VL level between 29th of October 2010 and 30th of March 2015, and his CD4 count levels fluctuated during this period between 294 and 356; his serum creatinine also reduced to normal.

He subsequently went on a one year drug holiday because he no longer had access to the third line regimen due to donor policy which no longer supported the provision of third line ARVs.

By January 2016, his CD4 cell count reduced to 7 cells/mm^3 (almost a year into the drug holiday). Another resistance test done on 6th of June 2016 on all the classes of ARVs, where he was found to be susceptible to all, he was then placed on Efavirenz (EFV), 3TC and TDF on the 9th of April 2016. On the 9th of June 2016 the Serum Creatinine levels had increased to 164 and CD4 cell count was 10 cells/mm^3.

This was in spite of 100% adherence, measured by pharmacy pick up records. By October 2016, he was able to privately procure Dolutegravir (DTG) and his regimen was switched to Abacavir, lamivudine and DTG. The last three tests done in 2016 are shown in **Table 2.**

Table 2: The last three tests done in 2016.

Date	VL (copies/ml)	CD4 (cells/mm^3)
25th January 2016	Not available	7
9th June 2016	210544	10
3rd December 2016	246137	20

Second patient

This is Mrs MB a female who presented for HIV treatment at the age of 39 years. She is a Civil Servant. Her date of birth is 29th of September 1966. She was pregnant at enrolment, married, had five children and neither drank alcohol nor smoked. Her husband and children appeared to be HIV negative at enrolment. Her GA at enrolment was 32 weeks. She was referred to our treatment centre from University of Nigeria teaching hospital. She had been on treatment for two and a half years. She was placed on NVP, Stavudine (d4T) and 3TC; this regimen was continued at enrolment at our site. Previous history showed she had been treated for Tuberculosis (TB) in 2004. She enrolled on the 2nd of June 2006. While she delivered via elective C-section on the 5th of June 2006. No complication, baby was alive and well.

On the 24th of August 2006 she was found to have TB and so had a drug substitution where NVP was stopped and EFV was commenced she was also started on Rifampicin(R), Isoniazid(INH), Ethambutol(E), Pyrazinamide(Z), and Intramuscular(I.M) Streptomycin. On the 24th of May 2007 she was discharged from the TB clinic (DOTS centre), INH prophylaxis was then given. EFV was discontinued and NVP was recommenced.

By 16th January 2008, patient was pregnant again and a diagnosis of immunologic treatment failure was made as CD4 cell count had declined from 141 cell/mm^3 in June 2006 to 22 cells/mm^3 in November 2007, adherence was assessed to be good by pharmacy pick up records. She was subsequently switched to second line regimen by March 2008 after routine pre-switch adherence counseling.

A year later (17th March 2009), patient was called to clinic for an unscheduled appointment due to a panic value CD4 cell count of 39 cell/mm^3 and Hb of 9.3 g/dl. Patient on consultation agreed to having productive cough of more than one month duration, fever, night sweat and weight loss. A diagnosis of relapse tuberculosis infection and immunologic failure to second line antiretroviral therapy was made. ART was stopped and she was immediately commenced on CAT II anti-TB therapy. A review of her case was presented to the Implementing partners and resistance testing was done.

A year later, based on results of the resistance testing, the implementing partners provided 3rd line ARVs and on 13th March 2010, she commenced the 3rd line regimen of Ritonavir 100 mg, Darunavir 600 mg, Etravirine 200 mg and Raltegravir 400 mg, all 12 hourly (two times daily). She was on this regimen till March 2015 when she no longer had access to the third line regimen due to donor policy which no longer supported the provision of third line ARVs, she subsequently went on a one year drug holiday. The Drug substitutions and Switches and tests that were done were shown in **Table 3.**

Table 3: The drug substitutions and switches and tests that were done.

Sl No.	Start date of new Regimen	New Regimen	Date of Tests	VL (copies/ml)	CD (cells/mm^3)
1	24th of August 2006	3TC,d4T,EFV*	2nd of June 2006	70832	141
2	19th of June 2007	3TC, AZT,NVP**	24th of February 2007	253232	278
3	13th of March 2008	LPV/r,TDF,3TC,AZT	22nd of November 2007	3288	22
			26th of March 2008	Not available	49
4	19th of March 2010	RTV,DRV,ETR,RAL***	20th of August 2009	11935	Not available
			17th of December 2010	200^	201
			18th of April 2011	Not available	118
			18th of July 2011	200^	208
			18th of October 2011	200^	256
			08th of June 2012	Not available	243
			24th of February 2012	253232	278
			08th of June 2012	Not available	243
			06th of September 2012	Not available	331
			12th of December 2012	Not available	92
			25th of April 2013	20^^	302

*She was started on TB medication hence the substitution.

**TB drugs were stopped.

***On the 22nd of June 2009 HIV-1 ARV drug resistance report showed that patient was susceptible to only DRV, while on the 28th of May 2009 she was recommenced on TB therapy but placed on Rifabutin to replace Rifampicin, Augmentin was added to the regimen.

^Detection limit<50 copies/ml

^^Detection limit<20 copies/ml

After one year of drug holiday, by March 2016, her CD4 cell count had declined to 9 cell/mm^3 and another resistance testing was done on the 17th of June 2016. The result showed virus to be susceptible to all protease inhibitors, Lamivudine and Emtricitabine.

It showed intermediate susceptibility to Abacavir, Tenofovir and Etravirine but resistant to all NNRTIs, Didanosine, Stavudine and Zidovudine. On the 21st of June 2016 patient was recommenced on ARV with ATV/r, 3TC, and ABC. Her CD4 cell count increased to 12 cell/mm^3 after 12 weeks on the new

regimen. Result showing subsequent CD4 and VL values shown in **Table 4.**

Table 4: Showing subsequent CD4 and VL values.

Date	VL (copies/ml)	CD4 (cells/mm^3)
30th January 2015	44	151
31st March 2016	429585	9
11th October 2016	130	102

Third patient

Mr WW a construction Engineer who was 39 years with date of birth 25th October 1952. His partner was not HIV positive. This patient was transferred from No 68 Nigerian Army Reference hospital to our centre on the third line regimen/ Salvage regimen. He had previously started ARV on the 20th of February 2001. His baseline result showed CD4 count 80 cells/mm^3 (done on 29th August 2005) and just before enrolment tests done on 9th November 2011 showed CD4 count 282 cells/mm^3 and VL was 764. Regimen at presentation was TDF, 3TC, DRV, RTV, ETR and RAL. He was enrolled on the 13th of February 2012. At enrolment CD4 count was 223 cells/mm^3 and just at the last visit it was 364 cells/mm^3 on the 5th of May 2014. Just before his last visit patient complained of Body aches which was treated with analgesics thereafter he did not come back to the clinic.

Discussion Perspectives on the Use of Third-line

There is limited experience with use of third line regimen in sub-Saharan Africa. Data is available from a few cohort studies done in South African but our literature search did not provide evidence of published data from Nigeria. The cases presented are to the best of our knowledge, the first such publication from Nigeria.

One of South African Cohort studies was presented by Michelle Moor house at the 2016 Southern African HIV Clinicians Society 3rd Biennial Conference. The presentation [10] enumerated the eligibility criteria for third line regimen to include: adult on protease inhibitor regimen who are not fully suppressed; who had genotype resistance test done; who had PI resistance and full treatment history presented to a panel for third line regimen; documented resistance to boosted PI an access to third line drugs including boosted Darunavir, Etravirine and Raltegravir. The first two cases presented in our report met the above criteria. The cases we have presented were on the same third-line regimen as the above South African Cohort and achieved 66.7% viral suppression while the South African cohort achieved 94% viral suppression. It is noteworthy that the 3rd case was lost to follow-up after 2 year while the other 2 were followed up for 4 years. Another South African retrospective cohort on third-line regimen reported earlier by Meintjes 7 achieved 71.1% viral suppression after a median of 2.5 years of follow up.

Conclusion

Third line regimen is effective but there is need to secure access. The cases reported had to interrupt treatment because access to free third-line ART was terminated by implementing partners. The Nigerian government is encouraged to take up the responsibility to provide third line regimen.

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